Reviewer's report

Title: Identification of novel KCNQ1 and KCNH2 mutations and the protective effect of KCNH2 SNP K897T in Long QT Syndrome families

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Reviewer: Tomas Novotny

Reviewer's report:

With a great interest I read the manuscript of Zhang, Chen et al and I really appreciate the amount of work and effort which must be behind it. The more I was dissapointed by confusing manner with which these interesting data are presented in the manuscript.

Major compulsory revisions:

1. While it is obvious these days that LQT syndrome is genetically very heterogenous disease, identification of some new mutations in LQT related genes is not surprising. Therefore such finding cannot be the leading theme of present-day article (unfortunately, since in all centers we have some yet undescribed mutations...). In my opinion the most important message of presented manuscript is the finding of mutation-SNP interaction in KCNH2 gene and its effect on QT interval. I strictly recommend to make this finding the leading theme of the article – from the title on throughout all the manuscript. Then, new mutations can be mentioned as a byproduct of the study.

2. Abstract: In Background paragraph there is no information on the aim of the study. The Methods paragraph is one long sentence – probably some punctuation is missing, therefore the sense is confused. Information on number of investigated individuals is missing. Results paragraph, line 5: „...interacts with mutation A490T in cis.“ The proper term is „cis orientation“. This should be corrected and unified throughout all the manuscript - the meaning of cis vs. trans orientation should be later briefly explained.

3. The last 10 lines of „Background“ contains rather results and conclusions. Therefore these statements should be omitted here and should be moved to corresponding sections of the manuscript.

4. The „Methods“ section should be organized as follows: Study subjects, clinical examination, DNA isolation, linkage, mutational and SSCP analyses.

5. Clinical diagnosis of LQTS is based on diagnostic score (Schwartz et al, Circulation 1993;88:782-4.). According to this score in a particular individual the diagnosis of LQT can be present with low, intermediate or high probability. Therefore it is not clear how the authors cosidered a particular individual as affected or non-affected. T wave morphology assessment is mentioned but it is not specified which classification was used.

6. ECG recording sweep and voltage should be specified. Since QT interval
values are presented with precision of 10 ms the supposed sweep must be at least 50 mm/s. Otherwise the precision of the measurement should be corrected.

7. In the „Methods“ there is no information on exercise test protocol and equipment and Holter ECG devices. It is also not clear if ECGs were evaluated by more than one physician (cardiologist?) and if he or she was aware of the diagnosis.

8. Results, Identification of a novel KCNQ1 mutation...: Numbers of investigated individuals are presented in confusing manner. It is not clear, how many family members were really examined by investigators. Results, paragraph 1, line 2: „Five affected members had a history of syncope.“ Is this number related to „...over 300 family members...“ mentioned in the line 1 of this paragraph or to „...forty-two family members...“ two lines below? Clinical characteristics of the investigated individuals is scattered throughout all the 4 paragraphs of this section. Some table would be helpful. In one case only abolute number are stated, in another case only percentage, while both numerical information are important. Results, paragraph 4, lines 3 and 4: „...age 33±22 yrs, 13 F)...“ – yrs means probably years, F – females – but these should be spelled out.

Results, paragraph 4, lines 7-10: while investigating 24 carriers vs. 4 non-carriers, it is highly problematic to compare statistically QTc in these very different groups. On the other side I wonder in how many mutation carriers the initially normal QTc did reach pathologic values during exercise test.

9. Results, Identification of two co-segregating variant..: this should be the leading theme of the article to be presented in the first place. But again: Immediately in the first line a family QW2648 is mentioned, but no other information on numbers or clinical characteristics are provided. In the next paragraph, line 5, it is stated that „...QTc was significantly prolonged (P=0.0002).“ Compared to whom? No information on exercise testing in non-carriers is provided. „Bradycardia was seen in five of seven carriers...“ Under which conditions? Resting ECG or else? Holter monitoring is mentioned in only 2 individuals showing bradycardias. There were no Holters in the other family members? If this is true then information on Holters should be omitted because when performed only in 2 family members it brings no experimentally relevant data, just 2 case reports.

10. Results, Identification of a novel 2-bp insertion mutation...: Author are describing a patient with depressed left ventricle function and left bundle branch block, who presented with VT (the term is not spelled out) with the need of cardioversion. Information on VT morphology is not provided (if it was monomorphic,then it is definitely not related to LQT syndrome). During Holter monitoring polymorphic ventricular ectopics were present and also runs (how long?) of polymorphic ventricular tachycardia (now the term is spelled out while an abbreviation could have been used yet). In my opinion in this patient a high probability of coronary artery disease is present, or dilated cardiomyopathy if the former is excluded. But this possibility was not excluded and even not mentioned (troponin level?, coronary angio is obligatory in such patient). I wonder how the authors did avoid an artificial QT prolongation in an individual with intraventricular conduction prolongation, QRS duration is not mentioned. In conclusion, if
presented in this manner, the association of the described mutation to LQT syndrome is highly problematic. A membrane electrophysiogy study is not available, is it?

11. Results, Identification of five other mutations…: I do not understand, why in patient with R366X mutation the clinical data are provided, while not in the others.

12. In all cases information on concomitant therapy is completely missing, concomitant diagnosis is described in only one case.

13. The „Discussion“ section is interesting, clearly written and well supported by data from literature. It clearly shows that the authors are aware of the most important message of their manuscript. Nevertheless I still have some comments: Page 10, line 11. It is not clear how „bradycardia phenotype“ was defined.

Page 10, line 12: The provided data do not clarify why authors consider residue A490 a mutation hotspot.

Page 11, line 4: If advantage of family based approach is stressed it is obligatory to consider also limitations.

14. No limitation of the presented study are mentioned throughout all the article!!!

15. Figure 1: „Individuals with uncertain LQTS diagnosis or without clinical data are shown in gray symbols.“ This should be distinguished to avoid confusion.

Minor compulsory revisions:
1. In title no abbreviations should be present, therefore „SNP“ should be spelled out.
2. In the abstract there should be „results“ instead of „result“.
3. Background, paragraph 2, line 2: The correct name of the gene is ANK2, not ANKB (it encodes a protein called ankyrin B).
4. P values should be expressed uniformly throughout the manuscript: either 0,01 or 1x10-2.
5. Measurement of ECG should be expressed in either seconds or milliseconds – this should be unified.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.